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*March 09, 2005*

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**APPLICATION NUMBER:** *60/544,604*
**FILING DATE:** *February 13, 2004*
**RELATED PCT APPLICATION NUMBER:** *PCT/US05/04533*

Certified by

Jon W. Dudas

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15750 U.S. PTO
021304

PTO/SB/16 (01-04)
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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

**Express Mail Label No.** ER 767989356 US

| INVENTOR(S) | | |
|---|---|---|
| Given Name (first and middle [if any]) | Family Name or Surname | Residence (City and either State or Foreign Country) |
| Steven B. | Harris | Rancho Cucamonga, California |

*Additional inventors are being named on the* one *separately numbered sheets attached hereto*

**TITLE OF THE INVENTION (500 characters max)**

A Microemulsion Preparation of High Concentration Propofol for Anesthetic Uses

*Direct all correspondence to:* **CORRESPONDENCE ADDRESS**

☐ Customer Number:

***OR***

| | | | | | |
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15535 U.S. PTO
60/544604
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**ENCLOSED APPLICATION PARTS *(check all that apply)***

☑ Specification *Number of Pages* 68
☐ CD(s), Number
☐ Drawing(s) *Number of Sheets*
☐ Other (specify)
☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.
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*Respectfully submitted,*

SIGNATURE

Date February 13, 2004

REGISTRATION NO. 37,147 *(if appropriate)*

Docket Number:

TYPED or PRINTED NAME Jay P. Hendrickson

TELEPHONE 415-884-9957

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|---|---|---|
| Given Name (first and middle [if any] ) | Family or Surname | Residence (City and either State or Foreign Country) |
| Nick J. | Huang | Rancho Cucamonga, Californis |



Number 2 of 2

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# FEE TRANSMITTAL for FY 2004

*Effective 10/01/2003. Patent fees are subject to annual revision.*

☑ Applicant claims small entity status. See 37 CFR 1.27

**TOTAL AMOUNT OF PAYMENT** ($) 80.00

| Complete if Known | |
|---|---|
| Application Number | |
| Filing Date | February 13, 2004 |
| First Named Inventor | Steven B. Harris |
| Examiner Name | |
| Art Unit | |
| Attorney Docket No. | |

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## FEE CALCULATION

### 1. BASIC FILING FEE

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1001 | 770 | 2001 | 385 | Utility filing fee | |
| 1002 | 340 | 2002 | 170 | Design filing fee | |
| 1003 | 530 | 2003 | 265 | Plant filing fee | |
| 1004 | 770 | 2004 | 385 | Reissue filing fee | |
| 1005 | 160 | 2005 | 80 | Provisional filing fee | 80.00 |

SUBTOTAL (1) ($) 80.00

### 2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

| | Extra Claims | | Fee from below | | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | | -20** = | | X | = |
| Independent Claims | | - 3** = | | X | = |
| Multiple Dependent | | | | | = |

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 1202 | 18 | 2202 | 9 | Claims in excess of 20 |
| 1201 | 86 | 2201 | 43 | Independent claims in excess of 3 |
| 1203 | 290 | 2203 | 145 | Multiple dependent claim, if not paid |
| 1204 | 86 | 2204 | 43 | ** Reissue independent claims over original patent |
| 1205 | 18 | 2205 | 9 | ** Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) ($)

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## FEE CALCULATION (continued)

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|---|---|---|---|---|---|
| 1051 | 130 | 2051 | 65 | Surcharge - late filing fee or oath | |
| 1052 | 50 | 2052 | 25 | Surcharge - late provisional filing fee or cover sheet | |
| 1053 | 130 | 1053 | 130 | Non-English specification | |
| 1812 | 2,520 | 1812 | 2,520 | For filing a request for *ex parte* reexamination | |
| 1804 | 920* | 1804 | 920* | Requesting publication of SIR prior to Examiner action | |
| 1805 | 1,840* | 1805 | 1,840* | Requesting publication of SIR after Examiner action | |
| 1251 | 110 | 2251 | 55 | Extension for reply within first month | |
| 1252 | 420 | 2252 | 210 | Extension for reply within second month | |
| 1253 | 950 | 2253 | 475 | Extension for reply within third month | |
| 1254 | 1,480 | 2254 | 740 | Extension for reply within fourth month | |
| 1255 | 2,010 | 2255 | 1,005 | Extension for reply within fifth month | |
| 1401 | 330 | 2401 | 165 | Notice of Appeal | |
| 1402 | 330 | 2402 | 165 | Filing a brief in support of an appeal | |
| 1403 | 290 | 2403 | 145 | Request for oral hearing | |
| 1451 | 1,510 | 1451 | 1,510 | Petition to institute a public use proceeding | |
| 1452 | 110 | 2452 | 55 | Petition to revive - unavoidable | |
| 1453 | 1,330 | 2453 | 665 | Petition to revive - unintentional | |
| 1501 | 1,330 | 2501 | 665 | Utility issue fee (or reissue) | |
| 1502 | 480 | 2502 | 240 | Design issue fee | |
| 1503 | 640 | 2503 | 320 | Plant issue fee | |
| 1460 | 130 | 1460 | 130 | Petitions to the Commissioner | |
| 1807 | 50 | 1807 | 50 | Processing fee under 37 CFR 1.17(q) | |
| 1806 | 180 | 1806 | 180 | Submission of Information Disclosure Stmt | |
| 8021 | 40 | 8021 | 40 | Recording each patent assignment per property (times number of properties) | |
| 1809 | 770 | 2809 | 385 | Filing a submission after final rejection (37 CFR 1.129(a)) | |
| 1810 | 770 | 2810 | 385 | For each additional invention to be examined (37 CFR 1.129(b)) | |
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| 1802 | 900 | 1802 | 900 | Request for expedited examination of a design application | |

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## SUBMITTED BY

(Complete *(if applicable)*)

| | | | | | |
|---|---|---|---|---|---|
| Name (Print/Type) | Jay P. Hendrickson | Registration No. (Attorney/Agent) | 37,147 | Telephone | 415 884 9957 |
| Signature | | | | Date | 2/13/04 |

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JAY P. HENDRICKSON
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February 13, 2004

**Mail Stop Provisional Patent Application**
Commissioner for Patents
P.O. Box 1450
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Re: Provisional Patent Application
For: A Microemulsion Preparation of High Concentration Propofol
Inventors: Steve B. Harris and Nick J. Huang
Filed: February 13, 2004

Sir:

Enclosed please find a Provisional Application for Patent Cover Sheet, Provisional Patent Application for the above-referenced provisional patent application, Fee Transmittal and a check in the sum of $80.00 for the filing fee.

Sincerely,

Jay P. Hendrickson
Reg. No. 37,147

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Jay P. Hendrickson

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2/13/04
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# PROVISIONAL PATENT APPLICATION

**FOR**

# A MICROEMULSION PREPARATION OF HIGH CONCENTRATION PROPOFOL FOR ANESTHETIC USES

**Inventors: Steven B. Harris**
**Nick J. Huang**

**Dated: February 13, 2004**

## A Microemulsion Preparation of High Concentration Propofol for Anesthetic Uses

**Abstract**: A method of producing physiologic saline or water-based optically clear microemulsions of the anesthetic propofol (2,6 diisopropylphenol) for use as an intravenous anesthetic agent in mammals is disclosed. The method relies only on the use of certain polyethylene glycol esters of fatty acids as emulsification agents. The method requires simple stirring and no complex agitation procedures. Certain hydrophobic cosolvents and ethanol are useful for improving the propofol drug loading capability of the microemulsions up to a drug content of about 10% of the total liquid weight. However, these extra ingredients are not required ingredients *per se* for making propofol microemulsions in saline up to 4% drug by total weight.

### TECHNICAL FIELD

The present invention relates to preparing a physiologically isotonic oil-in-water type microemulsion of the anesthetic propofol as a pharmaceutical for administration parenterally to mammals, for purposes of general anesthesia. Propofol (2,6 diisopropylphenol) is practically non-soluble in water, and must presently be delivered in low concentration (1% wt/v) oil-in-water emulsions of soybean oil. The present invention provides for manufacture of high concentrations (up to about 10%) of propofol emulsions in saline, suitable for surgical anesthesia induction in large and small mammals.

### BACKGROUND OF THE INVENTION

Systems for water dispersion of drug are necessary for intravenous administration of drugs which are not water soluble, and in particular are necessary for administration of the anesthetic propofol (2,6 diisopropyl phenol), a liquid which in its pure state is practically water-insoluble. Propofol is a long-known drug which as the pure chemical is inexpensive to produce, and which is presently used extensively in human and veterinary medicine as a general anesthetic agent. Propofol is capable of producing deep anesthesia which resolves in a comparatively short time (such as 15 minutes), after administration of the drug is stopped.

Presently, pharmaceutical propofol is prepared by dissolving it in soybean oil, then preparing an emulsion of this oil with egg phospholecithin, to a final concentration of about 10% soybean oil in saline, with concentration of the drug standardized to 1% of the total liquid preparation. These emulsions have a droplet size up to 200 nm and have the appearance of milk. They may be termed "macroemulsions." Such propofol emulsions, despite addition of preservatives, are similar to intravenous lipid nutritional preparations and are excellent growth media for bacteria. For this reason all propofol preparations in the U.S. have been restricted to single-patient-use vials and ampoules, with directions for discarding of penetrated containers within hours after first use.

Microemulsions are thermodynamically stable emulsions having droplet sizes that are too small (typically less than 100 nm) to scatter visible light, thus rendering them optically

transparent, similar to true chemical solutions. The smallest size microemulsions do not even exhibit optical opalescence. Microemulsions of the sought-after type assemble spontaneously from certain mixtures of surfactants, hydrophobic materials, and water, with only stirring, and no need for vigorous agitation such as sonication.

There is particular need for development of propofol microemulsions for pharmaceutical intravenous use, which would be optically clear and thus more indicative of contamination should contamination happen (bacteria scatter light). Also there is need for propofol preparations which are not as conducive to growth of bacteria and fungi when contaminated, as are the present oil and phospholecithin preparations. There is a need for propofol preparations containing far more than the 1% concentration presently commercially available, for use in larger animals. Finally, there is need for propofol preparations which are easily sterilized, as are the preparations described in this disclosure. The emulsifier Solutol HS-15 can be liquefied and heated under atmospheric pressure to 120 centigrade, which simple procedure sterilizes it and all drugs dissolved in it, such as propofol. The resultant sterile liquid can then be cooled and mixed into sterilized saline to form the microemulsion, with no further sterilization or treatment steps needed. If required, the resulting microemulsion can be further sterile-filtered at the 0.2 micrometer level. Microemulsions pass such filters much more easily than do current soybean oil macro emulsions (which pass bacterial filtration only with some difficulty).

Prior art has described emulsion systems for delivery of propofol, but has described ordinary opaque emulsions of the type which are presently used, and failed to specify methods for producing specifically only optically transparent microemulsions. Recently, general microemulsion systems for pharmaceutical delivery have been taught (US 6,602,511), but methods taught for making these are overly complicated, partially because an attempt has been made in these patents to cover all possible drugs and microemulsion delivery systems. Unfortunately for patents which attempt to cover the entire field, the best microemulsion system for each drug will vary with the drug which the system is intended to deliver.

For example, in US 6,602,511 (von Corswant August 5, 2003) describes preparation of pharmaceutical microemulsion systems, intended for drug delivery, which are comprised of (1) a polar phase with osmotic modifier such as physiologic saline, (2) a surfactant film modifier such as ethanol, (3) a non-polar phase consisting of at least one pharmaceutically acceptable oil and (4) and (5) a mixture of a hydrophilic and a hydrophobic surfactant up to 15% by weight of the total microemulsion (preferably 4-12%). US 6,602,511 covers surfactant concentrations up to 15% apparently because those over 15% are described as necessary in another microemulsion system in EP 334 777. Still other patents cover water in oil microemulsions, which are more useful in cosmetics than IV pharmaceutical applications.

In fact, the complex systems described in the above prior art are not necessary for the production of useful propofol microemulsions, as is inferentially taught by the inventors of US 6,602,511 as regards the supposedly general case of drug delivery by microemulsions. For example, as described below, a 1% propofol microemulsion in

saline, comparable in concentration and effect to the commercial preparation, may be made from nothing more than saline (q.s.), and a mixture of 1 part propofol and 10 or more parts of an appropriate emulsifier such as PEG-600 15-hydroxypropyl stearate ("Solutol HS-15" from BASF Corp, Germany), or for a second example, the similar molecule PEG-23 monostearate. The reason for the simplicity of this recipe is that, for lower concentrations of propofol, a surface modifier such as ethanol may be omitted, and propofol itself may serve as a hydrophobic material, without need for an oil or lipophilic solvent carrier. In fact, usable microemulsions of up to 4% propofol in saline can be made using nothing more than Solutol HS-15 (see example below).

Finally, we point out that for production of many useful and highly concentrated thermodynamically stable microemulsions, it is not necessary, as claimed in US 6,602,511, to employ a two-component hydrophobic/hydrophilic surfactant system. Instead, hydrocarbon-PEG surfactants are generally capable of forming microemulsions from immiscibly-hydrophobic liquids in water, though the loading factors are poor if the hydrocarbon is not a standard fatty acid and the PEG (polyethylene glycol) component is less than about 13 polymer units long.

A single-component surfactant system optimized for microemulsification of propofol distinguishes our method from more complex systems intended *a priori* to cover all hydrophobic drugs, such as are described in US 6,602,511. Our most concentrated propofol systems require a hydrophobic cosolvent and ethanol as described by US 6,602,511, but they remain distinguished by use of a single emulsifier of the PEG-fatty-acid-ester type.

## BRIEF DESCRIPTION OF THE INVENTION

The present invention is a novel method for making optically clear propofol microemulsions in saline, up to about 10% by weight propofol, and is effective for pharmaceutical purposes as an intravenous general anesthetic in mammals. The propofol microemulsions have been tested on dogs, cats, and horses and have been found to be just as effective as other commercial veterinary anesthetic products and, specifically, just as effective as conventional propofol in an oil-in-water based opaque "macro"emulsion.

The propofol microemulsions of the present invention show no evidence of pain on IV injection to the conscious animal. Although all conventional propofol preparations cause stinging when delivered subcutaneously or intramuscularly (this is believed to be a direct drug effect of propofol), the drug vehicle does influence tissue reaction to propofol emulsions delivered extra-venously. Conventional propofol preparations in soybean oil can cause tissue damage and harm if extravasated. By contrast, there is sign of tissue reaction to deliberately extravasted microemulsion material such as we describe, when it is placed in the forelimbs of dogs.

Finally the higher concentrations obtainable with the described propofol microemulsions, which are many times more concentrated than those attainable with present commercial techniques, are expected to be of particular use in the surgical anesthesia of the larger

mammals such as horses, cattle and also the larger exotic mammals. In experimental work with dogs using 10% propofol, and with horses using 5% propofol, the entire anesthetic dose of material could be rapidly injected (for example 1000 mg as 20 mL of 5% solution in 500 kg horses, or 2 mL of 10% solution = 200 mg in 25 kg dogs) before the animal becomes aware of beginning alteration in consciousness. The observed rapidity of onset of anesthesia for propofol after detection by the animal, which precludes time for extensive reaction or bolting motion by the animal, makes high concentration microemulsified propofol a superior drug for use in horses and other large mammals.

## DESCRIPTION OF THE INVENTION

In general the present invention consists of methods to make microemulsions of liquid propofol, using PEG-containing surfactants, preferably the low-viscosity PEG-ester surfactant Solutol HS-15 (BASF Corp). It is preferred in all uses that the liquid propofol be pre-mixed with 1% vitamin E (free alpha tocopherol) to prevent oxidation in liquid solution. This vitamin E preserved drug is meant whenever "propofol" is mentioned below. In order to be intravenously compatible, emulsions must be carried in a water phase which is isotonic to blood, such as 0.9% saline, 5% dextrose, or other crystalloid or colloid containing isotonic solutions intended for intravenous administration, as will be obvious to those skilled in the art.

Because of the relatively lower viscosity of high concentration Solutol HS-15 solutions, it is a preferred microemulsion agent for high concentrations of microemulsified drug. The observed drug loading factor for a stable Solutol HS-15 based microemulsion is also about 40% higher than for the similar PEG-23-monostearate, suggesting that the loading factor for PEG esters is approximately dependent on a mole fraction basis (PEG-23-monostearate is approximately 40% higher in molecular weight than Solutol HS-15). For lower propofol concentrations in saline (below about 4% propofol) it is preferable to keep the ratio of Solutol HS-15 to propofol above 8 to 1. This insures a completely clear microemulsion, with no hint of opalescence, at any additional dilution with saline.

Propofol microemulsions of suitable viscosity for injection, containing up to 10% propofol, are obtained using Solutol HS-15 at lower ratios to propofol, with assistance of ethanol or C-3 alcohols, and a suitable liquid hydrophilic cosolvent of low viscosity. These microemulsions are clear when mixed, but show a very faint opalescense on simple dilution with large amounts of saline, due to the fact that they require Solutol HS-15 to propofol ratios less than 8 to 1. Suitable hydrophobic cosolvent liquids which will permit higher concentrations of drug in microemulsions to at least 10% of total volume (with Solutol HS-15 concentrations in the range of 30% so as not to exceed maximal solution viscosity for injection), include ethyl oleate (preferred), medium chain triglyceride (MCT) oil, and benzyl acetate. Typically ethanol is used in a weight ratio of about 1 part alcohol to 5 parts Solutol HS-15 (for ethyl oleate containing emulsions), and the lipophilic cosolvent such as ethyl oleate is used in a ratio of 1 part cosolvent to 10 parts Solutol HS-15 (preferred ratio).

For the cosolvent, the possible use of many other candidate physiologically compatible liquid esters of 4 to 24 carbons (ethyl acetate to myristyl myristate) will be obvious to those skilled in the art. We have used ethyl oleate or MCT oil specifically because they are already approved for IV human use, as is Solutol HS-15. Benzyl acetate has been used because its benzylic structure is expected to be unusually compatible with the benzylic structure of propofol.

Finally, since the propofol microemulsions are optically clear, several systems for coloring the clear IV are feasible, producing products which are easily distinguishable by eye, so that accidents involving solutions of similar appearance but different anesthetic concentrations, are more easily avoided. We have successfully used I.V. compatible preparations of fluorescein dye (yellow), methylene blue dye (blue), and a combination of these (which produces a lipid-soluble green dye) to color various microemulsified propofol solutions. Use of other medically compatible dyes will occur to those skilled in the art, for production of other colors, such as vitamin B12 to be used for primary red.

**PREFERRED EXAMPLES**

**Example #1. Propofol 1% (weight/volume = w/v) microemulsion in saline using PEG-23 monostearate alone.** One gram of PEG-23 hydroxymonostearate is heated in a 20 mL glass bottle enough to melt the surfactant, after which it is mixed with 100 mg propofol. Before this mixture can solidify, 9 mL of warm physiologic saline is mixed in to give a final microemulsion containing 1% propofol by weight. This emulsion is optically transparent, and colored very pale yellow from the propofol. This solution is comparable to the commercial 1% propofol product, but contains no soy or egg products to support microbial growth.

**Example #2. Propofol 4% (w/v) microemulsion in saline using Solutol HS-15 alone.** To make 4% propofol, 3.2 grams of Solutol HS-15 is melted as previous described, and 400 mg propofol added and mixed to form the emulsion base. Then warm saline is slowly mixed into the emulsion base. After addition of 4 mL of saline, a characteristic gel forms, characteristic of the bicontinuous fluid resulting from about equal weights of water and emulsification agent. After a total of 6.4 mL saline is added, a total of 10 mL of freely-flowing optically clear microemulsion of drug in water is obtained, which is 32% by weight Solutol HS-15. Such emulsions and solutions containing about 30% Solutol-HS, are of low enough viscosity for intravenous injection without pain, according to the pharmacological literature on Solutol HS-15. The described emulsion is 4% weight/volume propofol (4 times the present standard commercial concentration) and is found to be suitable for direct injection intravenously, as also are all the Solutol HS-15 based microemulsions described below.

**Example #3: Anesthesia of a dog with microemulsion prepared in Example #2.** A 30.5 kg animal had been pre-treated with 25 mg acepromazine and 0.2 mg atropine. He was conscious with eyes open, but sedated when injected with 3 ml (120 mg propofol = about 4 mg/kg) of the 4% propofol solution from example #2, directly into a foreleg vein. Within 30 seconds the dog was fully relaxed and was rapidly assessed at level 3, plane 2

anesthesia, with no blink reflex, inability to hold jaw closed, and no gag on endotracheal intubation. Apnea lasted 15 seconds, then spontaneous breathing began. The animal tolerated the endotracheal tube for 35 minutes before opening eyes and beginning gag behavior, necessitating tube removal. The animal was fully recovered within one hour.

When the same animal was treated identically on the following day, but without acepromazine or atropine pre-treatment, he showed consciousness and gag at 12 minutes post anesthetic administration. When given intravenously to a fully conscious animal without pretreatment, this microemulsion was observed during injection to cause no effect before unconsiousness, save brief tongue-licking (we believe indicative of the animal tasting the anesthetic). The animal showed no evidence of nausea/vomiting, or IV injection pain.

**Example #4. Preparation of propofol 10% (w/v) microemulsion in saline using Solutol HS-15, ethanol, and ethyl oleate as hydrophobic cosolvent.** To make 10% propofol microemulsion, 3.0 grams of Solutol HS-15 is melted as previous described, and 1.0 mg propofol, 0.3 g ethyl oleate, and 0.6 gram ethanol added and mixed to form the emulsion base. Then warm saline is slowly mixed into the emulsion base. After addition of 5.1 mL of saline, a total of 10 mL of freely-flowing optically clear microemulsion of drug in water is obtained, which is 30% by weight Solutol HS-15. The described emulsion is 10% by weight propofol (10 times the commercial concentration) and is found to be suitable for direct injection intravenously.

MCT oil and benzyl acetate at the same weight as ethyl oleate may replace ethyl oleate in this 10% preparation, although for these cosolvents an equal weight ratio of ethanol to propofol must typically be used, for the highest concentrations of propofol such as 10% w/v. Thus, 3.0 grams Solutol, 1.0 gram of propofol, 1.0 gram of ethanol, 0.3 g of MCT and 4.7 g of saline would be used in the mixture above, to obtain a 10% propofol microemulsion using MCT.

**Example #5. Anesthesia of a dog with 10% w/v microemulsion prepared in Example #4 using ethyl oleate.** A 23.3 kg animal was not pretreated. He was injected with 1.5 ml (150 mg propofol = about 6 mg/kg) of the 10% propofol solution from example #4, directly into a foreleg vein. Within 30 seconds the dog relaxed and was rapidly assessed at level 3, plane 2 anesthesia, with no blink reflex, inability to hold jaw closed, and no gag on endotracheal intubation. No apnea was noted. The animal tolerated the endotracheal tube for 11 minutes before opening eyes and beginning gag behavior, necessitating tube removal. The animal lifted his head at 15 minutes after being given anesthesia.

**Example #6. Preparation of 5% propofol w/v microemulsion in saline using Solutol HS-15, ethanol, and ethyl oleate as hydrophobic cosolvent.** To make 5% propofol, 2.5 grams of Solutol HS-15 is melted as previous described, and 0.5 g propofol added, 0.25 g ethyl oleate, and 0.5 gram ethanol added and mixed to form the emulsion base. Then warm saline is slowly mixed into the emulsion base. After addition of 6.25 mL of saline,

a total of 10 mL of freely-flowing optically clear microemulsion of 5% drug in water is obtained, which is 25% by weight Solutol HS-15. This is suitable for injection.

**Example #7. Preparation of 3% (w/v) propofol microemulsion in saline using Solutol HS-15, ethanol, and ethyl oleate as hydrophobic cosolvent.** To make 3% propofol microemulsion which is suitable for further dilution with complete clarity and no opalescence, to lower concentrations such as 2% or 1%, the following method is used: 2.4 grams of Solutol HS-15 is melted as previous described, and 0.3 g propofol added, 0.15 g ethyl oleate, and 0.3 gram ethanol added and mixed to form the emulsion base. Then warm saline is slowly mixed into the emulsion base. After addition of 6.85 mL of saline, a total of 10 mL of freely-flowing optically clear microemulsion of 3% drug in water is obtained, which is 24% by weight Solutol HS-15. This is suitable for injection. Further dilutions to 2% or 1% drug (w/v), as is used below, may be made by simple addition of saline to this solution.

**Example #8. Anesthesia of a dog with 1% (w/v) propofol microemulsion, prepared as in Example #7 using MCT in place of ethyl oleate, then diluted with saline.** To make lower concentrations of propofol, one part of the microemulsion of **Example #4** or the equivalent made with MCT in place of ethyl oleate, may be appropriately diluted with 3 parts saline to a final propfol concentration of 1%. Microemulsions of greater than 4 % propofol typically exhibit brief cloudiness on adding saline, which resolves and again becomes opalescent on mixing. Properly constructed microemulsions of less than 3% propofol as in Example #7, which have a higher ratio of Solutol to propofol, typically remain completely optically transparent after dilution and mixing.

Such microemulsions are stable to the eye, with or without refrigeration, for at least 8 weeks. Such a 1% propofol microemulsion was made as in **Example #4** but replacing ethyl oleate with MCT, and finally diluted to 1% propofol content with saline. A 15.4 kg dog pre-treated with acepromazine 15 mg and atropine 0.2 mg exhibited a 15 minute span between anesthesia and gag reflex return, after being given 70 mg (7 mL = about 3 mg/mL) of this 1% propofol preparation by I.V. This is indistinguishable to doses of propofol anesthetic needed, and typical response to them, when commercially available 1% propofol preparations are used in dogs.